delivering the identifying agent through at least one breast duct in an amount sufficient to detect lymph node involvement;

determining the lymph node involvement after said coupled compound has been delivered in said at least one breast duct; and

identifying the location of said lymph node involvement.

REMARKS

Examiner Rawlings and Examiner Wortman are thanked for the courtesies extended to the undersigned and Ms. Firestone during the interview of July 16, 2001.

The Office Actions of March 9, 2001 and November 16, 2001 have been received and considered. In the Office Action of March 9, 2001, claims 1-16 were rejected under 35 U.S.C. §112 and either 35 U.S.C. §102(b) or 35 U.S.C. §103(a). Claims 17-32 were withdrawn from consideration. In the Office Action of November 16, 2001, it was explained that the amendment filed September 10, 2001 was not fully responsive because the marked-up version of claim 5 did not show all of the made changes.

Claims 1, 5, 9 and 13 have been amended. A revised marked-up copy of the amended claims is attached. Claims 17-32 have been deleted. Claims 1-16 remain pending. Reconsideration of the application is respectfully requested.

Claims 9-16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification so as to enable one skilled in the art to which it pertains to make and/or use the invention. This rejection raises two issues. Specifically, the Office Action asserts that the specification does not teach: (1) how can one distinguish from the lymph nodes identified by an agent as including a lesion or tumor and the remaining lymph nodes that are also mapped by an

applied agent; and (2) the steps of invasively obtaining and removing particular cells for histopathologic examination as taught by the prior art. The rejection also suggests that the present invention is a method of identifying a sentinel lymph node by injecting an identifying agent into a lumen of an affected breast duct of a patient diagnosed with cancer to facilitate surgical excision of the sentinel lymph node. Hence, the position is taken that steps regarding histopathologic examination of excised tissue must be disclosed in order for lymph node involvement to be determined.

The present invention relates to **in vivo** determinations of the presence of cancerous or precancerous cells by specifically identifying only the location of a cancerous or precancerous cell and, if present, the location of a lesion. The agents used in the present invention only mark the presence of one or more cancerous cells, precancerous cells and/or lesions. Therefore, the methods according to the present invention do not identify the remainder of the breast duct or the sentinel lymph nodes that would be identified by conventional nodal mapping. Hence, the advantages of the present invention eliminate the need for biopsies used with the prior art methods to determine if the cells in question or a lesion are present. Additionally, the introduced agents eliminate the need for invasively obtaining cells in order to determine if the cells in question are cancerous or precancerous and/or if a lesion is present.

The method of the present invention delivers targeting agent(s) coupled to identifying and/or therapeutic molecules into the ductal network by introducing them directly through an associated ductal opening in a nipple. Targeting agents include those discussed extensively in the specification. The targeting agent cells bind to lesion cells and display limited or preferably no binding to epithelial cells and ductal lining cells.

The targeting agents bind the cancerous or precancerous cells and allow contact of these cells with the cytotoxic agent that may be conjugated to the therapeutic agent. However, the targeting agents disclosed in the instant specification will not bind to the healthy epithelial cells within the ductal network. As a result, nonspecific binding and nonspecific cytotoxic activity is avoided because contact between the healthy cells and the cytotoxic agent is avoided.

As discussed on page 12, lines 15-24, the identifying agents also identify lesions to the sentinel nodes and thus the method of the present invention is more accurate than conventional surgical methods. An advantage of the method of determining lymph node involvement according to the present invention includes the focused release of the agent in the vicinity of the lesion, rather than throughout the entire ductal network as done with methylene blue, etc. This controlled release provides a more precise identification of lymph nodes most likely to drain a particular lesion. At page 12, lines 23 and 24, the specification expressly teaches that the method according to the present invention provides a level of tumor or lesion staging previously unobtainable without an invasive or surgical procedure.

Contrary to the position taken in the Office Action, the methods recited in claims 9-16 specifically eliminate the need for the invasively obtaining and removing steps of cells for histopathologic examination discussed in the outstanding rejection because it uses the natural, inherent functioning of the lymph nodes to determine the lymph node involvement. The natural function of the lymph nodes is to receive fluid from within the duct and allow it to pass into and through the node before draining into other parts of the body. As a result, by introducing the above-discussed agents directly into the duct, these

agents will bind only the cancerous cells or lesions before passing through the lymph nodes and draining into the body. Hence, when a sentinel lymph node has a lesion, the cancer specific agent will bind it and identify its presence. For those nodes without a lesion, the agents will flow through them and not leave any indicator. As a result, a need to invasively determine the lymph node involvement is not needed because only those nodes with a lesion will have a bound agent.

For all of the above-discussed reasons, applicants submit that the methods recited in claims 9-16 are fully enabled by the present specification.

Claims 1, 5, 9 and 13 have been amended to include the "whereby" phrases set forth in the Office Action. Claims 1, 5, 9 and 13 have also been amended to change the phrase "preselected individual duct" to "at least one". This amendment overcomes the objection to the term "preselected" and broadens the scope of these claims so that the method encompasses those methods in which the duct is not "preselected". Also, this amendment also overcomes the objection to the word "individual" and the use of the phrase "more than one duct" in particular dependent claims. The use of the phrase "at least one" provides claims 1, 5, 9 and 13 with the breadth that is appropriate for the dependent claims (3, 7, 12 and 16) that recite the "more than one duct". As clearly understood, claims 1, 5, 9 and 13 are now clearly broader than 3, 7, 12 and 16, respectively. For the above-discussed reasons, the rejections of claims 1, 5, 9 and 13 should be withdrawn.

Claims 1-16 have also been rejected for not including, what are suggested to be, one or more essential steps. These steps are listed in the Office Action. Applicants submit that the steps in question are not essential as "essential matter" is defined in

MPEP §2172.01. Essential matter is not merely those elements or steps that form a portion of the invention. Instead, "essential matter" is defined in M.P.E.P. §2172.01 as elements, steps or the like that are described by the applicant(s) in the specification as essential to practicing the invention. Therefore, in order for a step in the method to be considered essential matter, the applicant(s) must have disclosed in the specification that this step was "essential" to the practicing of the invention. This is not the case in the instant application. Applicants have not indicated that any of the steps recited in the Office Action are "essential" to the method as "essential" is defined in the M.P.E.P. Therefore, these steps cannot fairly be considered essential and the rejection should be withdrawn.

Claims 5-8 were rejected under 35 U.S.C. §102(b) as being clearly anticipated Hou et al. (Hou) as evidenced by VanZee et al. (VanZee). Hou discloses a method of performing galactography before excision in patients with nipple discharge. During the galactography method discussed in Hou, a discharging breast duct is identified and a contrast material is introduced into this duct. Then, a mammogram is performed on the patient. When the mammogram indicates that a duct should be removed due the presence of premalignant or malignant cells, methylene blue is introduced into the breast duct via a catheter to identify the boundary of the duct containing the cell(s). The methylene blue stains the entire duct so that a surgeon can identify, locate and remove the entire duct. The methylene blue is not a cancer specific agent as recited in amended claim 5. Therefore, the step of introducing the methylene blue into the duct does not anticipate the step of "providing a premalignant or malignant cancer cell specific identifying agent" as recited in claim 5. Withdrawal of the rejection is requested.

Claims 1-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hou in view of Allan et al. (Allan) and Vitetta et al. (Vitetta) as evidenced by Krag et al. As discussed above, Hou discloses a method of performing galactography on a patient. In the Hou method, the contrast material is introduced into the duct before the mammogram is performed. If the mammogram identifies that a surgical excision of a duct is necessary, methylene blue is introduced into the breast duct in question. After the introduction of the methylene blue, a precise surgical excision of the dye-stained ducts and lobules is performed. The methylene blue only maps the duct to be removed by the invasive surgical procedure. The methylene blue is not a targeting molecule coupled to an identifying agent that identifies the cancerous cells. Similarly, the methylene blue is not a cancer specific agent. Instead, it is only a dye that identifies the shape of the duct to be removed.

Allan discloses a method of radioimmunolocalization of a breast duct to facilitate surgical excision of tissue including and surrounding malignant breast cancer cells. The Office Action suggests that it would have been obvious to modify the method of Hou with the step of introducing the agent of Allan into the breast duct through a ductal opening. However, as discussed below, this modification would not have been obvious because at least (1) no motivation exists for the asserted combination, (2) impermissible hindsight has been used to pick and choose portions of the Allan method while ignoring others, (3) no expectation of success exists for this modification and (4) the steps needed to prepare the agent disclosed in Allan's method contradict the method set forth in Hou.

In order to perform the method disclosed in Allan, the patient is first subjected to a mammogram. Then, if the mammogram identifies questionable cells, fine needle

aspiration (FNA) or a core biopsy is performed on the tumor in the breast. As is well known in the art, FNA is a very uncomfortable procedure for the patient and can lead to the spreading of cancerous cells within the body. After the FNA or biopsy has been performed, the collected samples are analyzed. An antibody based on the fine needle aspirate is then developed. The developed antibody is then systemically introduced into the body.

As discussed during the interview, it would not have been obvious to one of ordinary skill in the art to modify the method of Hou by only substituting the identifying agent of Hou with the antibody prepared by the method of Allan. First, the step of systemically introducing the antibody of Allan cannot be ignored. Allan has to be taken as a whole. Allan teaches that the developed antibody is introduced systemically into the body. Without some teaching in the prior art for introducing the antibody through a breast duct opening, no motivation exists for introducing the antibody into the patient anyway but systemically. The prior art does not teach the step of introducing a cancer specific agent into a breast through a breast duct. Similarly, it does not provide any expectation of success for such a modification. The most the cited references teach regarding intraductal introduction is the infusion of a contrasting agent and a mapping dye that identifies the boundary of the breast duct.

Additionally, Allan's teaching of systemically introducing an antibody into a patient would not have motivated one of ordinary skill in the art to modify the introduction of a contrast material or methylene blue (used only to identify the duct that is being entirely removed) into a breast through a breast duct to arrive at the method recited in claims 1-16. No motivation exists for this combination in the prior art.

Additionally, no expectation of success exists for the suggested modification in view of the prior art teachings. Applicants submit that only their own specification provides motivation and expectation of success for this combination. Thus, they also submit that the outstanding rejection is based on impermissible hindsight. Absent some teaching in the prior art and expectation of success, the rejection cannot be sustained.

The rejection is also not sustainable for the following reasons. The method of Hou requires the mammogram to be performed after the identifying agent - contrast material - has been introduced into the breast duct. To the contrary, the steps of the Allan method require that the mammogram be performed before the agent is developed so that the tumor accessed during the FNA step can be located. The modification suggested in the Office Action would require that the steps of the Hou method be modified so that the mammogram of Hou is performed before the agent used in the Hou mammogram is prepared and introduced into the body. The mammogram of Hou cannot be performed without its identifying agent - its contrast material. This modification contradicts the teachings of Hou and would render its method inoperable. Therefore, such a modification would not have been obvious to one of ordinary skill in the art.

Like the disclosures of Hou and Allan, the disclosure of Vitetta et al. (Vitetta) does not teach introducing a targeting molecule coupled to an identifying agent or a cancer specific identifying agent into a breast through a breast duct. Therefore, like Allan, Vitetta would not have motivated one of ordinary skill to modify the method of Hou to arrive at the methods recited in claims 1-16. For all of the above-discussed reasons, withdrawal of the rejection is requested.

Claims 1-16 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 6,168,779 to Barsky et al. (Barsky) in view of Allan. as evidenced by Krag et al. and the internet contents of "oncologychannel.com."[1]

Barsky is directed to and discloses a method of identifying ductal orifices on a nipple surface. While Barsky does include a statement that diagnostic, therapeutic or other materials could be instilled into the duct, Barsky does not disclose or contemplate a method of identifying the location of premalignant or malignant breast cancer within a breast duct or ductal network as recited in claims 1-16. Hence it cannot disclose such a method that includes the step of delivering either a targeting molecule coupled to an identifying agent or a cancer specific identifying agent into a breast through a breast duct.

The disclosures relied upon in the Office Action on columns 3 and 4 of the Barsky patent relate to the location and identification of ductal openings. These disclosures do not and cannot be fairly considered to disclose steps for determining if the epithelial lining of the duct includes premalignant or malignant cells. These disclosures are limited to their specific teaching of ductal opening identification. The very broad interpretation of these statements set forth in the Office Action cannot be sustained when the patent is taken as a whole.

As discussed above, Allan discloses a method for systemically introducing an antibody into a patient for locating cancerous cells within the body. Allan does not disclose that the antibody can be introduced into the patient other than systemically. Neither reference provides any teaching of providing the recited targeting molecule and

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[1] The oncologychannel.com document is not prior art and cannot be used in this rejection. The reference was downloaded in March of 2001. This date is one year and five months after the date that the instant application was filed. Therefore, this document is not prior art to the present application.

identifying agent or cancer specific agent into the breast by intraductal introduction. Therefore, Allan would not have motivated one of ordinary skill in the art to modify the method of detecting ductal orifices on the nipple surface with a method of systemically introducing an antibody into a patient to detect the presence of cancerous cells. No teaching exists in either Barsky or Allan that would have lead one of ordinary skill to modify the method of Barsky to arrive at the method recited in claims 1-16. Additionally, there is no expectation of success for the asserted combination. Withdrawal of the rejection is requested.

For all of the above-discussed reasons, Applicants respectfully submit that claims 1-16 are allowable and that the application is now in condition for allowance. A notice to this effect is earnestly solicited.

If any questions or issues remain, the resolution of which the Examiner feels would be advanced by a conference with Applicants' attorney, the Examiner is invited to contact Applicants' attorney at the number noted below.

Respectfully submitted,

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Marked-Up Version of Amended Claims for 09/410,336

1. (Amended) A method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising:

providing a targeting molecule coupled to an identifying agent; [and]

delivering the coupled compound through at least one [a preselected individual] breast duct in an amount sufficient to identify premalignant or malignant cancerous cells; and

identifying the location of the premalignant or malignant cancer within the at least one breast duct after the coupled compound has been delivered within the at least one duct.

5. (Amended) A method of identifying the location of premalignant or malignant breast cancer within a breast duct or breast ductal network, said method comprising:

providing a premalignant or malignant cancer cell specific identifying agent; [and]

delivering the identifying agent through at least one [a preselected individual] breast duct in an amount sufficient to identify premalignant or malignant cancerous cells; and

identifying the location of the premalignant or malignant cancerous cells within the at least one breast duct after the coupled compound has been delivered within the at least one duct.

9. (Amended) A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising:

providing an identifying agent coupled to a targeting agent; [and]

delivering the coupled compound through at least one [a preselected individual] breast duct in an amount sufficient to detect lymph node involvement;

determining the lymph node involvement after said coupled compound has been delivered in said at least one breast duct; and

identifying the location of said lymph node involvement.

13. (Amended) A method of determining the lymph node involvement in patients diagnosed with premalignant or malignant breast cancer growths, said method comprising:

providing an identifying agent; [and]

delivering the identifying agent through at least one [a preselected individual] breast duct in an amount sufficient to detect lymph node involvement;

determining the lymph node involvement after said coupled compound has been delivered in said at least one breast duct; and

identifying the location of said lymph node involvement.